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THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of the Application and Complete Specification filed on 10/08/2004 in respect of Patent Application No.861/MUM/2004 of (a) M/S. IPCA LABORATORIES LIMITED, (b) 48, Kandivli Industrial Estate, Mumbai - 400 067, Maharashtra, India (c) Indian company incorporated under the Companies Act 1956.

This certificate is issued under the powers vested in me under Section 147 (1) of the Patents Act, 1970.

Dated this 11th day of July 2005.

(A.T. PATRE)

ASSTT. CONTROLLER OF PATENTS & DESIGNS

FORM 1

THE PATENTS ACT, 1970

(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

[See section 5(2), 7, 54 and 135; rule 39]

1. We,

(a) **M/S. IPCA LABORATORIES LIMITED**

(b) **48, Kandivli Industrial Estate, Mumbai – 400 067, Maharashtra, India**

(c) **Indian company incorporated under the Companies Act 1956**

2. Hereby declare –

(a) that we are in possession of an invention titled “**An improved industrial process for manufacture of methyl (±)-α-(2-chlorophenyl)-4,5,6,7-tetrahydrothieno [3,2-C] pyridine-5-acetate**”

(b) that the Complete Specification relating to this invention is filed with this application.

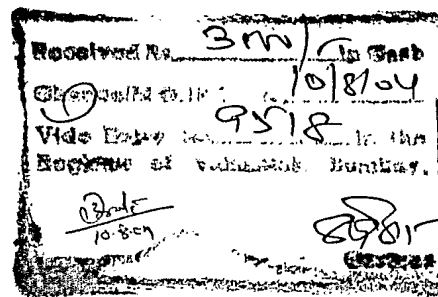
(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventor(s) for the said invention are

(a) **Kumar, Ashok**

(b) **A4/203 - 4, Sterling CHS,
Sundaravan Complex,
Andheri (West)
Mumbai - 400 053
Maharashtra, India**

(c) **Indian National**



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ORIGINAL

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- (c) Indian National

- (a) **Burudkar, Sandeep Madhavrao**
- (b) Survey No.17/A, Harinagar,
Ramwadi,
Pune – 411 014,
Maharashtra, India
- (c) Indian National

4. That we are the assignee(s) of the true and first inventors.

5. That our address for service in India is as follows:

**GOPAKUMAR NAIR ASSOCIATES, NAIR BAUG, AKURLI
ROAD, KANDIVLI (EAST), MUMBAI – 400 101.**

6. Following declaration was given by the inventor(s) :

We the true and first inventors for this invention in the convention country declare that the applicant(s) herein are our assignee

(Kumar Ashok)

(Bhayani, Priti Jayesh)

(Kushawaha, Lavkesh Dayashankar)

(Burudkar, Sandeep Madhavrao)

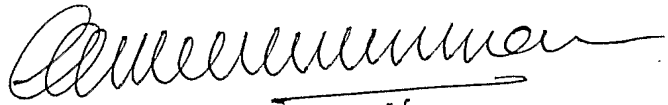
7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Following are the attachment with the application:

- (a) Complete specification (2 copies)
- (b) Statement and Undertaking on Form 3
- (c) Form 26 (Original power of attorney in our favour has been submitted with application no. 150/MUM/2003)
- (d) Fee Rs.3000/- in cheque bearing No.179365 dated 5th August, 2004 on HDFC Bank, Kandivli (E), Mumbai.

We request that a patent may be granted to us for the said invention.

Dated this 9th Day of August, 2004



Dr. Gopakumar G. Nair
Agent for the Applicant
GOPAKUMAR NAIR ASSOCIATES
Nair Baug, Akurli Road,
Kandivli (East), Mumbai – 400 101

To
The Controller of Patent
The Patent Office
At Mumbai

FORM 2

**THE PATENTS ACT, 1970
(39 of 1970)**

**COMPLETE SPECIFICATION
[See section 10, rule 13]**

“An improved industrial process for manufacture of methyl (±)-α-(2-chlorophenyl)-4,5,6,7-tetrahydrothieno [3,2-C] pyridine-5-acetate”

- (a) IPCA LABORATORIES LTD.**
- (b) 48, Kandivli Industrial Estate, Mumbai – 400 067, Maharashtra, India**
- (c) Indian Company incorporated under the Companies Act 1956**

The following specification describes the nature of this invention and the manner in which it is to be performed:

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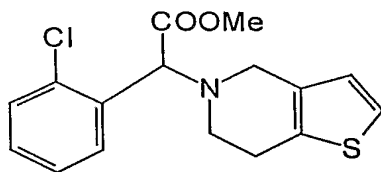
ORIGINAL

Technical Field of Invention:

This invention relates to an improved process for manufacturing α -2-(chlorophenyl)-6,7-dihydrothieno [3,2-C] pyridine-5 (4-H)-acetic acid methyl ester of Formula I, commonly known as Clopidogrel.

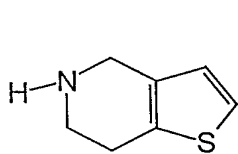
Background of the invention:

Clopidogrel is known for its platelet aggregating and antithrombotic properties and finds medicinal applications in this field. It can be represented by Formula-I, and was disclosed in Patent US 4529596 (hereinafter referred as '596' patent) in its racemic form for the first time.

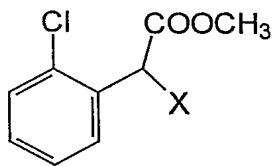


Formula I

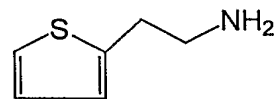
The '596' patent provides a synthesis of the said molecule of Formula I by the reaction of a thienopyridine derivative of Formula II with a chloro compound of Formula III (where X = Cl) in solvents like dimethyl formamide, alcohols and ethyl acetate in presence of alkali metal carbonates. However, it does not suggest preparation / source of the starting material, tetrahydrothienopyridine derivative, of Formula II.



Formula II



X = Cl or Br
Formula III



Formula IV

In a subsequent patent, JP 63101385, a convenient process for the preparation of the 4,5,6,7-tetrahydrothieno (3,2-c) pyridine intermediate (Formula II) was disclosed. According to the multi-step process of this patent, a commercially available 2-(2-thienyl) ethylamine (Formula IV) was reacted with formaldehyde to give an intermediate 2-(2-thienyl) ethyl formimine which was isolated and cyclized in presence of dry HCl in polar solvents to give the 4,5,6,7-tetrahydrothieno (3,2-c) pyridine of Formula II.

A similar process was disclosed in United States Patent 5132435 for the preparation of Clopidogrel by using the same reactants per se to yield the 4,5,6,7-tetrahydrothieno (3,2-c) pyridine derivative (Formula II) and reacting the same with a bromo-derivative of Formula III ($X = Br$) in solvents selected from alcoholic solvents, DMF, ether solvents and ethyl acetate in presence of alkali metal carbonate as the base. In the process, 2-(2-thienyl) ethylamine was reacted with formalin solution in water by heating to a temperature range of 70°C to 90°C and isolated the 2-(2-thienyl) ethyl formimine by a long procedure in pure form. This was reacted with dry hydrochloric acid solution in dimethylformamide to form the cyclized product (Formula II).

In these entire prior art the reactants per se are same but employ varying conditions to achieve better purity or yield. Although some of the problems are solved by modifying the reaction conditions or route of synthesis as taught by the prior art, there still exist problems like polymerization of intermediates which need to be investigated.

The cyclisation of the intermediate 2-(2-thienyl) ethyl formimine does not take place in presence of water. If water is present in the reaction it necessitates the isolation of formimine intermediate in pure form. This increases the number of operations and makes process plant unfriendly from industrial scale-up point of view. Moreover, the isolated intermediate, 2-(2-thienyl) ethyl formimine, is not a stable compound and polymerizes to give a trimer which makes it difficult to store / handle in normal conditions.

Although, the reaction of bromo-compound (Formula III) with 4,5,6,7-tetrahydrothieno (3,2-c) pyridine of Formula II gave moderate yields in the reported processes, the reactions takes long time for completion at temperature 60°C to 90°C as reported in '435' patent.

Carrying out reactions at above temperatures, that too for longer period, lead to formation of various impurities due to the lack of selectivity of reactions or decomposition of the reactants or products, which necessitates extra purification resulting into yield losses and increase in number of operations not desirable for a practical process. The search for a manufacturing process for the preparation of Clopidogrel employing easy synthetic methods resulting in a satisfactory yield / purity of final product remains undoubtedly of interest.

Objectives of the present invention:

It is, therefore, an objective of the present invention to provide an industrially useful process for the manufacture of Clopidogrel from starting materials that are readily and commercially available, relatively inexpensive, and easily maneuvered at large scale operations.

Other major objectives of this invention are

1. to provide a single pot conversion process for unstable intermediate 2-(2-thienyl)ethyl formimine formed in the reaction to a stable product of Formula II.
2. to design a process for preparation of Clopidogrel wherein the condensation of halo ester stage is performed under ambient conditions with accelerated rate of reaction.
3. to provide, optionally, a one-pot processes for the preparation of racemic Clopidogrel starting from 2-(2-thienyl)ethylamine.

Summary of the invention

Accordingly, there is provided a process for the manufacture of Clopidogrel starting from 2-(2-thienyl) ethylamine, which eliminates the isolation of an unstable intermediate like 2-(2-thienyl) ethyl formimine by subjecting it to a one pot cyclization to get 4,5,6,7-tetrahydrothieno (3,2-c) pyridine of Formula II.

In another aspect of the present invention, the 4,5,6,7-tetrahydrothieno (3,2-c) pyridine is reacted with halo-compound of Formula III (where X is Cl or Br) at room temperature in a solvent like water and/or ethylene dichloride (EDC) in presence of organic or inorganic bases like sodium carbonate.

In further embodiment of the invention, the 2-(2-thienyl) ethylamine is reacted with paraformaldehyde in solvents such as hydrocarbon solvents including aliphatic, aromatic and chlorinated hydrocarbon solvents and removing the water formed, azeotropically during reaction. The 2-(2-thienyl) ethyl formimine solution is cyclized in a single pot by supplying dry HCl gas / solution.

In yet another embodiment, the reaction of Formula II with Formula III is carried out in a combination of solvents like water and chlorinated hydrocarbon solvents at room temperature.

In yet another embodiment, the production of Clopidogrel is carried out in a single pot by reacting 2-(2-thienyl) ethylamine with paraformaldehyde in organic solvents, azeotropically removing water formed in the reactor, cyclizing the 2-(2-thienyl) ethyl formimine by supplying dry HCl gas/solution, and reacting the 4,5,6,7-tetrahydrothieno (3,2-c) pyridine formed with a solution of haloester (Formula III, where X = Cl or Br) in water or organic solvent or its mixtures thereof in presence of a base.

In the above said process, the Clopidogrel formed in the reaction is isolated by phase separation and by the removal of organic solvent. It is purified in solvents like acetone by forming hydrogen sulphate salt.

Brief Description of drawings

Figure 1. represents Powder X-Ray diffraction pattern (PXRD) of clopidogrel hydrogen sulphate Form I prepared according to example 6 of the present invention.

Figure 2. represents Differential Scanning Calorimetry record of Form I of clopidogrel hydrogen sulphate prepared according to example 6 of the present invention.

Figure 3. represents the spectrogram obtained by Fourier Transform Infra Red spectrometry (FTIR) of clopidogrel hydrogen sulphate Form I prepared according to example 6 of the present invention

Detailed description of the invention:

It has now been found that new condition / process makes it possible to convert 2-(2-thienyl) ethylamine to 4,5,6,7-tetrahydrothieno (3,2-c) pyridine via 2-(2-thienyl) ethyl formimine in a single step in one-pot and thereby eliminating the isolation of unstable intermediate, 2-(2-thienyl) ethyl formimine, making the process industrially more feasible.

Consequently, the invention relates to an improved synthesis of Clopidogrel by reacting 2-(2-thienyl) ethylamine with paraformaldehyde in presence of dry HCl, optionally isolating the compound of Formula II, and reacting with halo-compound of Formula III (X = Cl or Br) in a single organic solvent or a combination of organic solvents and water.

According to one aspect of the present invention, the 2-(2-thienyl) ethylamine is reacted with paraformaldehyde in a suitable solvent selected from non-polar solvent like aliphatic and aromatic hydrocarbon solvents, chlorinated hydrocarbons like dichloroethane (EDC) etc. The reaction takes place at a temperature of 30°C to 100°C

and the water formed as a byproduct in the reaction is removed continuously by azeotropic distillation using a Dean-Stark assembly. Azeotropic distillation herein means removal of two or more solvents from a mixture of solvents that form a low boiling mixture called azeotrope by distillation at elevated temperature.

After removal of water, the intermediate 2-(2-thienyl) ethyl formimine formed in the solvent is *in situ* reacted with dry HCl gas. The dry HCl also can be advantageously introduced into reactor as a solution in a suitable solvent. The solvent used for this purpose include dimethyl formamide, alcoholic solvents like methanol, ethanol, isopropyl alcohol etc. The one pot conversion of 2-(2-thienyl) ethylamine takes place in a period of 4 to 8 hours. The preferred temperature for carrying out the cyclization of intermediate in presence of the acid catalyst is in the range from 60°C to 90°C.

According to present invention, the cyclization of 2-(2-thienyl) ethyl formimine obtained takes place *in-situ* spontaneously in presence of acid and yields the stable intermediate 4,5,6,7-tetrahydrothieno (3,2-c) pyridine as its hydrochloride salt. The said salt precipitates from the reaction medium and conveniently isolated in substantially pure form.

The acid catalyzed cyclization of 2-(2-thienyl) ethyl formimine is carried out at a temperature range of 70°C to 75°C, preferably at 70°C for a period of 4 hours.

According to a preferred embodiment of the invention, 4,5,6,7-tetrahydrothieno (3,2-c) pyridine as a free base or its hydrochloride salt form is reacted with a halo derivative of Formula III in an organic solvent especially dichloroethane in presence of an organic base to obtain Clopidogrel. The organic base for carrying out this step of the process is selected from the group consisting of trialkyl amines such as triethylamine, trimethylamine, diisopropylethylamine and the like. The preferred base is triethylamine. The preferred halo derivative of Formula III is the bromo compound (Formula III, where X = Br).

According to the above process step of the present invention, the reaction is carried out at a temperature range of about 50°C to about 80°C for about 4 to 4.5 hours, preferably about 3.5 hours at 70°C. In this step of the process, where the acid salt of Formula II is used as reactant, then an excess amount of the base is used. This is required to neutralize the acid salt to liberate the free base of the compound of Formula II that reacts, with the halo derivatives of Formula III.

In another embodiment of the invention wherein, 4,5,6,7-tetrahydrothieno(3,2-c)pyridine is reacted with a halo compound of Formula III in a heterogeneous mixture of solvents selected from a combination of water and chlorinated hydrocarbon solvents such as dichloromethane or dichloroethane. The preferred solvent is a mixture of water and dichloroethane. The preferred ratio of water and dichloroethane is 1: 0.5

The base for carrying out the above process step is selected from the group consisting of inorganic bases like alkali metal carbonates. The preferred alkali metal carbonate used is sodium carbonate or potassium carbonate.

Preferably the inorganic base may be used in molar equivalent ratio relative to the halo compound of Formula III or in slight excess. In the case of reaction of acid salt of Formula II with Formula III, an excess base is used to liberate the free amine from acid salt. A preferable ratio of base used in this case ranges from 2 moles to 3 moles relative to compound of Formula II.

In this step of the process, the 4,5,6,7-tetrahydrothieno(3,2-c)pyridine or its hydrochloride salt and the inorganic base is taken in water in reaction vessel. The addition of a compound of Formula III is carried out as its solution in dichloroethane to form the heterogeneous reaction conditions. This process is particularly advantageous from the point of view of handling the halo compound of Formula III, due to its highly irritant and lachrymator properties.

According to the process of the present invention, this step is advantageously carried out at ambient temperature. Although the reaction goes faster at high temperature, to limit the impurity generation, this step is carried out at a temperature of 25°C to 30°C for a period of 7 to 10 hours, preferably 10 hours.

The Clopidogrel prepared following the above method is isolated by phase separation and washing the organic layer with water. The organic layer is removed by evaporation and the clopidogrel base obtained is purified in acetone by making its hydrogen sulphate salt. The pure Clopidogrel hydrogen sulphate is isolated as pure crystals from the solvent by suction filtration and drying.

According to a particularly advantageous alternative form of the present invention, the preparation of Clopidogrel may be carried out via 4,5,6,7-tetrahydrothieno (3,2-c) pyridine intermediate in the actual medium (hydrocarbon solvents) in which it is prepared in a single pot.

Consequently, according to the invention, clopidogrel is prepared by the following reaction in a single pot.

1. 2-(2-thienyl)ethylamine is reacted with paraformaldehyde in suitable solvent as described earlier and removing the water formed in the reaction azeotropically.
2. introducing dry HCl in the form of solution or gas and cyclizing the corresponding formimine to give 4,5,6,7-tetrahydrothieno(3,2-c)pyridine as hydrochloride in the reaction vessel.
3. saponifying the hydrochloride salt of 4,5,6,7-tetrahydrothieno(3,2-c)pyridine of Formula II with introduction of an aqueous solution of sodium or potassium carbonate in required amounts.
4. introducing halo-compound of Formula III as such or as a solution in organic solvent used for the stage 1 and reacting at a temperature of 25°C to 30°C for a period of 8 to 10 hours, preferably 10 hours,

5. isolating the Clopidogrel base in the organic layer after phase separation and washing with water, removing the solvent by evaporation to leave Clopidogrel base as residue in the reaction vessel, and
6. isolating pure Clopidogrel hydrogen sulphate by introducing acetone and conc. sulphuric acid into the reaction vessel.

The addition of Sulphuric acid is carried out preferably at a temperature of 0°C to 25°C and the addition of Sulphuric acid to the acetone solution of Clopidogrel base may be carried out in a controlled manner so as to avoid under exothermicity with proper cooling.

The Clopidogrel base obtained by the process of the present invention is, further, resolved into its enantiomers using optically active camphorsulphonic acid. The process of resolution involves contacting Clopidogrel base with (-) camphor sulphonic acid in a mixture of solvent like acetone and dichloromethane and crystallizing the dextroisomer as a diastereomeric salt of camphor sulphonic salt. The proportion of the solvent system (acetone: dichloromethane) used for the resolution is in the range of 10: 0.25 and preferably in a ratio of 10 : 1.0.

The diastereomer salt is then hydrolyzed using alkali metal carbonates such as sodium carbonate or ammonia to liberate the dextro enantiomer of Clopidogrel as free base. After hydrolysis, (+) Clopidogrel base was isolated by extraction using organic solvents like dichloromethane followed by evaporation of solvent to give (+) Clopidogrel having an enantiomeric purity > 99.5% and an yield of 76 to 80%.

The dextro-rotatory Clopidogrel base obtained above is converted into Clopidogrel hydrogen sulphate by salt formation with sulphuric acid in a solvent like ethyl acetate. The crystal form of Clopidogrel hydrogen sulphate isolated on crystallization is identified as Polymorphic Form I.

The following examples further illustrate the present invention but are not construed limiting in any manner to the scope of the invention as substantially described.

Examples :

Example 1 : One pot process for 4,5,6,7-tetrahydrothieno(3,2-C)pyridine hydrochloride.

100 gm. of 2-thienylethylamine was charged in a 1 litre reaction vessel equipped with a dean stark assembly for azeotropic removal of water. Dichloroethane (600 ml.) was added and the mixture stirred for 5 minutes. 26.4 gm. paraformaldehyde was added and the reaction mass was heated to reflux. Water formed in the reaction was continuously removed. After 4 hours the reaction mass was cooled to 30°C and 133 ml. of 6.6N hydrochloric acid solution in dimethyl formamide was added. The reaction mass was heated to 70°C for 4 hours. The reaction cooled to 15°C and filtered under suction and washed with dichloroethane. The solid obtained was dried in oven at 50°C. 124 gm (90%) of 4,5,6,7-tetrahydrothieno(3,2-c)pyridine hydrochloride are obtained.

Example 2 : Clopidogrel base and clopidogrel hydrogen sulphate (dichloroethane as solvent)

50 gm. 4,5,6,7-tetrahydrothieno(3,2-C)pyridine hydrochloride was charged in 1 litre reaction vessel. 150 ml. dichloroethane was added and stirred for 5 minutes. 75 gm. of methyl-1-bromo-(2-chlorophenyl)acetate and 80 ml. triethyl amine was added. Stirred at 25°C for 1 hour and then heated to reflux for 4 hours. The reaction mixture cooled to room temperature and quenched in water. The organic layer was washed with water, and distilled the dichloroethane to obtain clopidogrel base as an oil.

This clopidogrel base was dissolved in 300 ml. acetone and mixed with 17.5 ml. Conc. Sulphuric acid under cooling. The precipitated pure Clopidogrel hydrogen sulphate was

filtered and washed with acetone. The precipitate was dried in an oven at 50°C and 105 gm. (88%) Clopidogrel hydrogen sulphate was obtained.

Example 3: Clopidogrel base and Clopidogrel hydrogen sulphate (water and dichloroethane as reaction medium)

50 gm. of 4,5,6,7-tetrahydrothieno(3,2-C)pyridine hydrochloride was charged in 1 litre reaction vessel containing 500 ml. water and 75.4 gm. sodium carbonate and stirred for 1 hour. 75 gm. of methyl-1-bromo-(2-chlorophenyl) acetate in 250 ml. dichloroethane was added, stirred at 25°C for 8 hours. The organic layer was separated and washed with water, and distilled the dichloroethane to obtain Clopidogrel base as an oil.

This was dissolved in acetone (300 ml.), cooled to 0-5°C and mixed with 17.5 ml. conc. Sulphuric acid under cooling. The precipitated pure Clopidogrel hydrogen sulphate was filtered and washed with acetone. The precipitate was dried in an oven at 50°C. The 105 gm. (88%) Clopidogrel hydrogen sulphate was obtained.

Example 4 : One-pot process for Clopidogrel hydrogen sulphate from thienoethylamine

100 gm. of 2(2-thienyl)ethylamine was charged in a reaction vessel equipped with a dean-stark assembly for azeotropic removal of water. Dichloroethane (600 ml.) was added and the mixture stirred for 5 minutes. 26.4 gm. paraformaldehyde was added and the reaction mass was heated to reflux. Water formed in the reaction was continuously removed in 4 hours. The reaction mass was cooled to 30°C and 133 ml. of 6.6 N hydrochloric acid solution in dimethyl formamide was added. The reaction mass was heated at 70°C for 4 hours. The reaction cooled to 25°C and an aqueous solution of sodium carbonate (prepared from 1400 ml. water and 208 gms sodium carbonate) was added. The mixture was stirred for 1 hour and a solution of 206.7 gm. of methyl-1-bromo-(2-chlorophenyl) acetate in 690 ml. dichloroethane was added. The reaction mass stirred at room temperature for 9 hours and the aqueous layer is discarded. The organic layer washed with water and dichloroethane was evaporated. To the oil left in the

reaction vessel, 825 ml acetone was added and stirred for 1 hour. The mass cooled to 0 to 5°C and 48 ml. conc. Sulphuric acid was added. The mixture was further stirred for 4 hours. The precipitated crystals filtered off under suction and the pure Clopidogrel hydrogen sulphate was dried in oven at 50°C to get 280.5 gm (85%).

Example 5 : (S)(+) clopidogrel base.

93.0 gm (0.28 mole) of racemic base methyl-2- (2-chlorophenyl)-2-(4,5,6,7-tetrahydrothieno [3,2-c] pyridin-5-yl) acetate was charged in 550 ml mixture of acetone and dichloromethane solvent. 73.8 gm (0.31 mole) levo - camphor -10-sulphonic acid was added in the solution. The clear solution was stirred overnight at $30 \pm 2^\circ\text{C}$ and cooled the reaction mass to -2 to 3°C . The crystals obtained was filtered and washed with acetone and dried at room temperature under vacuum to give 61 gm of diastereomeric salt of (S)clopidogrel . The yield obtained is 76.0% on the basis of the starting racemate charged. The crystals have

$[\alpha]_D^{20} +25.25$ (c = 1.89%, methanol) ; HPLC (AGP^(R) column) assay = 99.65%.

The diastereomeric salt (60 gm) obtained above was dissolved in 240 ml water containing 16.8 gms of Sodium bicarbonate and 240 ml ethyl acetate was added and stirred for a period of 2 hours at room temperature. The organic layer was separated and washed with water and evaporated to give 35.35 gm of (+)-(S)- Clopidogrel base as an oil.

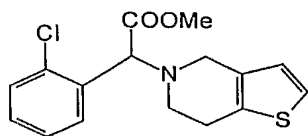
Example 6 : (S)(+) clopidogrel hydrogen sulphate polymorph Form I

Clopidogrel base (5.79 kgs) was dissolved in ethyl acetate (30 liters) at room temperature. This mixture was cooled to 18° C and concentrated sulphuric acid (96%, density = 1.83) was added (1.02 liters) maintaining temperature 18° to 20° C while addition. The reaction mass was stirred for 30 minutes and warmed slowly to 28° to 30°

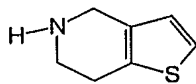
C in 30 to 40 minutes. The formed crystals were stirred for 8 hours. The solid obtained was filtered under suction and washed with ethyl acetate, and dried in oven at 48° C for 3 hours. The solid after drying weighed 6.7 kgs (88%) was Form I clopidogrel hydrogen sulphate (PXRD pattern incorporated: figure 1)

We claim,

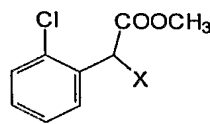
1. An improved industrial process for manufacture of Clopidogrel of Formula I starting from 2-(2-thienyl)ethylamine characterized in that the said process comprising



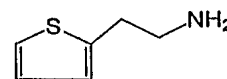
Formula I



Formula II



X = Cl or Br
Formula III



Formula IV

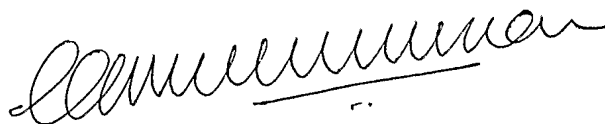
- i) a one-pot conversion of 2-(2-thienyl)ethylamine (IV) by the action of paraformaldehyde and anhydrous hydrochloric acid in a single vessel without isolation of 2-(2-thienyl)ethyl formimine intermediate into 4,5,6,7-tetrahydrothieno(3,2-c)pyridine intermediate of formula II, and
 - ii) reacting the said intermediate with halo benzene derivative of Formula III in presence of a base in solvent selected from dichloroethane or a mixture of water and hydrocarbon solvents under milder conditions and isolating clopidogrel as free base or hydrogen sulphate salt.
2. The process as claimed in claim 1 wherein, one-pot reaction of 2-(2-thienyl)ethylamine with paraformaldehyde and hydrochloric acid is performed in hydrocarbon solvents selected from aliphatic, aromatic hydrocarbons and chlorinated hydrocarbons, preferably dichloroethane.
 3. The process as claimed in claim 1 wherein, 2-(2-thienyl)ethyl formimine is formed in-situ by effective removal of water at reflux temperature and cyclized in presence of acid catalyst

4. The process as claimed in claim 1 wherein, the one-pot acid catalyzed cyclization of the intermediate 2-(2-thienyl)ethyl formimine is carried out at a temperature ranging from 60°C to 90°C.
5. The process as claimed in claim 1 wherein, 4,5,6,7-tetrahydrothieno(3,2-c)pyridine intermediate is isolated as its hydrochloride salt.
6. The process as claimed in claim 1, wherein reaction of 4,5,6,7-tetrahydrothieno(3,2-c)pyridine of formula II with halobenzene derivative of Formula III is carried out in dichloroethane.
7. The process as claimed in claim 6 wherein, the base is selected from trialkyl amines, preferably triethylamine.
8. The process as claimed in claim 6, wherein, reaction is performed at a temperature of 50°C to 80°C.
9. The process as claimed in claim 1 wherein, reaction of 4,5,6,7-tetrahydrothieno(3,2-c)pyridine of formula II with halobenzene derivative of Formula III is carried out in a heterogeneous solvents mixture.
10. The process as claimed in claim 9 wherein, reaction of 4,5,6,7-tetrahydrothieno(3,2-C)pyridine hydrochloride of formula II with halobenzene derivative of Formula III is carried out in water or in a mixture of water and hydrocarbon solvents selected from aliphatic, aromatic and chlorinated hydrocarbons.
11. The process as claimed in claim 9 and 10 wherein, the base is sodium carbonate or potassium carbonate.

12. The process is claimed in claim 9 wherein, reaction is performed at a temperature of 20°C to 40°C.
13. The process as claimed in claim 1 wherein, the Clopidogrel hydrogen sulphate is prepared in a one-pot procedure without isolation of intermediates comprising an acid catalyzed cyclization of 2-(2-thienyl)ethylamine with paraformaldehyde to form 4,5,6,7-tetrahydrothieno(3,2-c)pyridine of Formula II as hydrochloride, reacting the said compound of Formula II *in-situ* with a compound of Formula III in presence of base, and isolating Clopidogrel as hydrogen sulphate salt.
14. The process as claimed in claim 13 wherein, the base is sodium carbonate or potassium carbonate.
15. The process as claimed in claim 13 wherein, the reaction of compound of Formula II and compound of Formula III is performed in solvent selected from a mixture of water and water immiscible organic solvents.
16. The process as claimed in claim 15 wherein, the reaction is performed at a temperature of 20°C to 40°C.
17. The process as claimed in claim 1 wherein, the halo derivative of Formula III is preferably methyl-1-bromo-(2-chlorophenyl)acetate.
18. The process as claimed in claim 1 wherein, the Clopidogrel is isolated by forming hydrogen sulphate salt in acetone.
19. The process as claimed in claim 1 wherein, the Clopidogrel obtained is racemic Clopidogrel hydrogen sulphate.

20. The process as claimed in claim 1 further comprising the resolution of racemic Clopidogrel with levo-rotatory camphor sulphonic acid in a solvent system selected from a mixture of acetone and dichloromethane.
21. The process as claimed in claim 20 wherein, the proportion of acetone and dichloromethane is 10: 1.0
22. The process as claimed in claim 1, or 13 wherein, crystal form of the isolated Clopidogrel hydrogen sulphate is polymorph Form I.
23. An improved industrial process for manufacture of Clopidogrel of Formula I and its polymorphic form I as substantially described herein with reference to the foregoing examples 1 to 6.

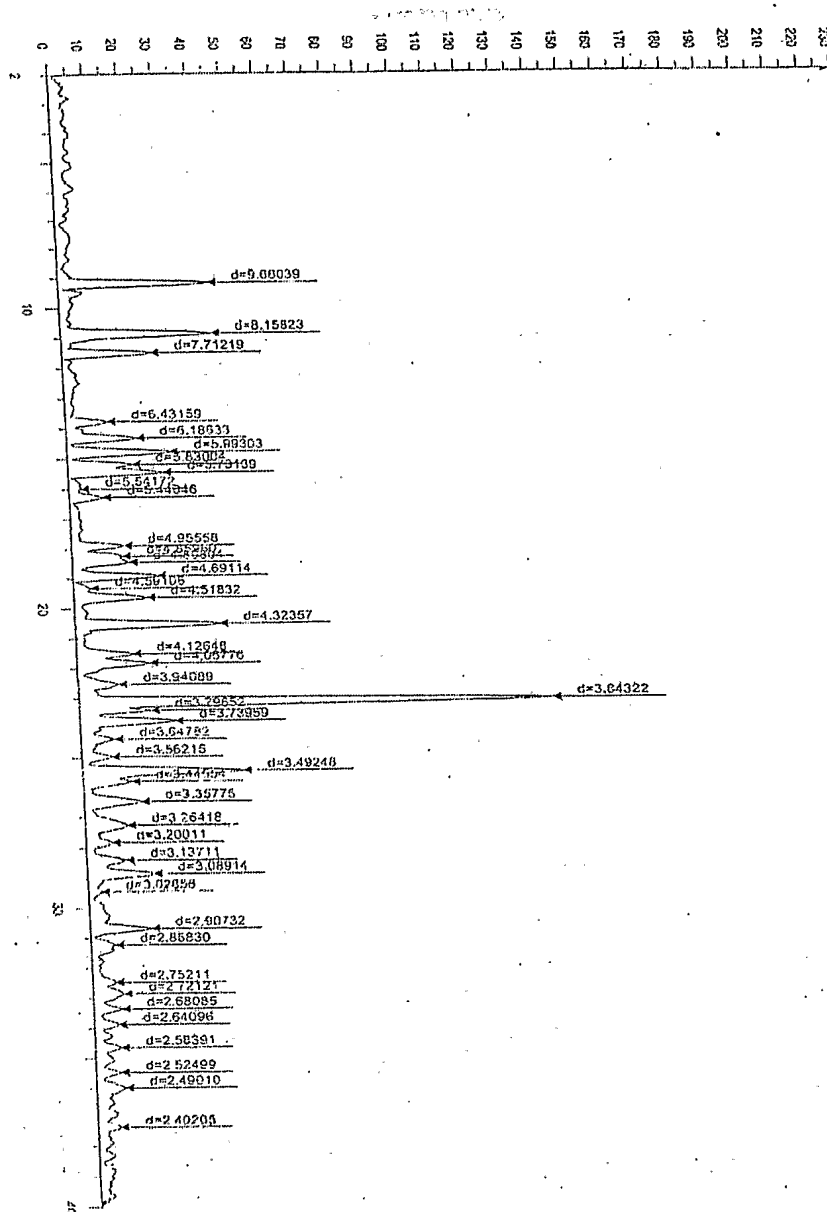
Dated this the 9th August 2004



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Application No.: /MUM/2004

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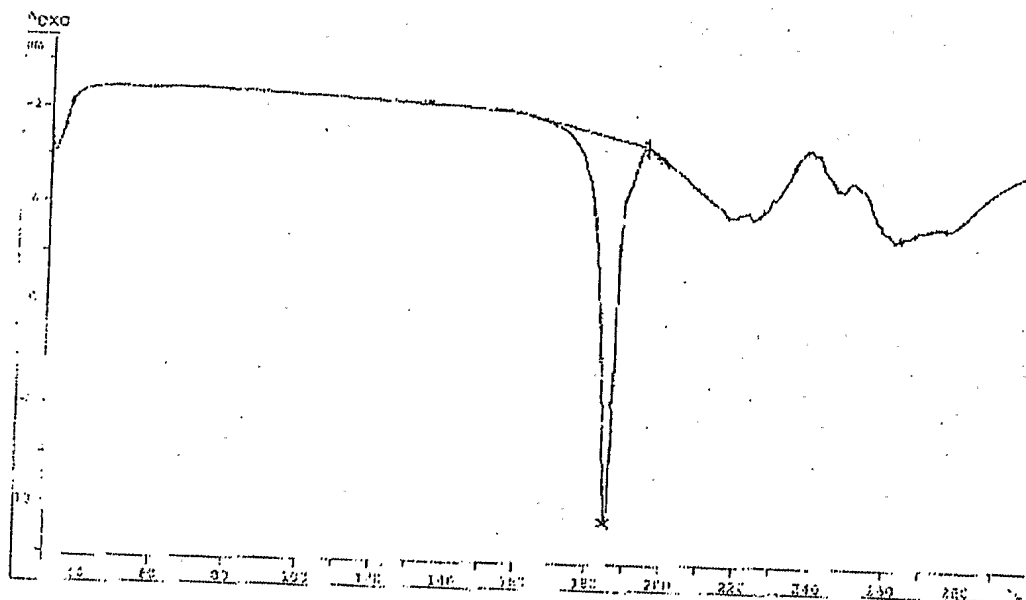


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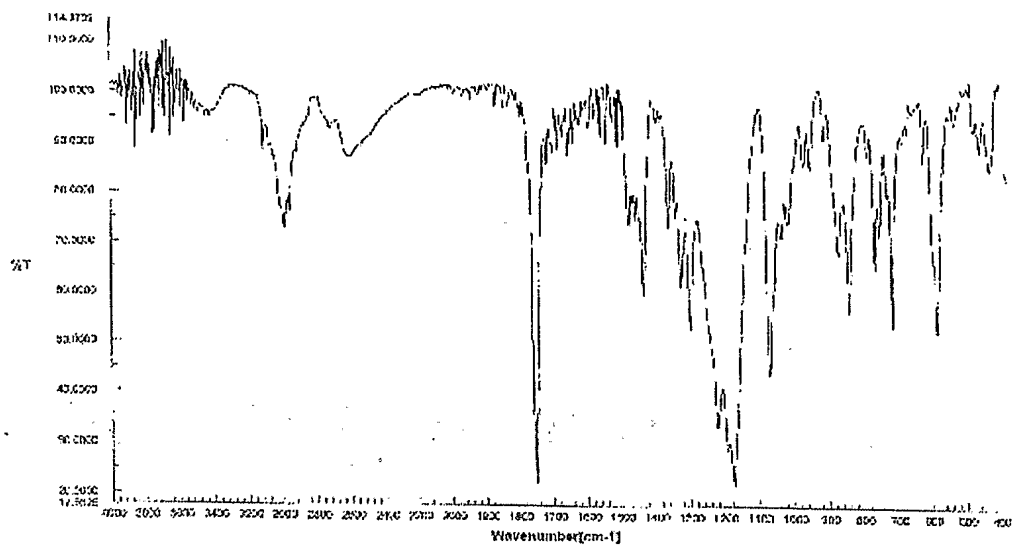
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Sheet No.2



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Sheet No.3



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